

## PATENT SPECIFICATION

696405



Date of Application and filing Complete Specification: Nov. 30, 1951.

No. 28132/51.

Application made In United States of America on Dec. 15, 1950.

Complete Specification Published: Aug. 26, 1953.

Index at acceptance:—Class 81(i), B11b2(g: i).

## COMPLETE SPECIFICATION

## Improvements in or relating to Preparations for Muscular and Nervous Disorders and Method of Preparing the same

We, CALIFORNIA INSTITUTE RESEARCH FOUNDATION, a corporation organised under the laws of the State of California, United States of America, of 1201 E. 5 California Street, City of Pasadena State of California, United States of America, (Assignees of HENRY BORSOOK and MANNIE E. BORSOOK), do hereby declare the invention, for which we pray that a 10 patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 15 therapeutic compositions and methods of making the same.

The present invention provides a therapeutic composition comprising a mixture of glycocyamine and at least an 20 equal molar quantity, per mole of glycocyamine, of a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.

The present invention also provides a 25 method of preparing a new therapeutic composition which comprises mixing glycocyamine and at least an equal molar quantity, per mole of glycocyamine, of a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.

The present invention further provides a method of preparing a therapeutic composition which comprises suspending in 35 a liquid medium, glycocyamine and at least an equal molar quantity, per mole of glycocyamine, of a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.

It is well established that creatine in 40 the form of phosphocreatine is a source of energy for the muscles and nerve cells of the human body. It has been found that in patients suffering from muscular 45 diseases the amount of phosphocreatine available in muscles, as measured by the

amount of creatinine in the urine, is less than that found in the muscles of a normal person. We have found that, by making available to the patient the 50 physiological precursors of creatine, marked improvement has been obtained in the condition of the muscles. We have further found that in order to obtain this improvement it is necessary to furnish 55 much greater amounts of creatine-producing material than are required by a healthy person.

We have found that glycocyamine may be methylated *in vivo* by compounds or 60 methylating agents such as choline, betaine, betaine hydrate and dimethylthetine to form creatine. The creatine thus formed passes to all tissues of the body and is 65 combined with physiologically available phosphate to form phosphocreatine, an available source of energy for the muscles and nerve tissues. During the course of our researches, we have also found that, 70 while methionine is a methylating agent for glycocyamine, it is not suitable for use in human therapy, since in the amounts required methionine has a toxic effect on the human body. 75

The following examples are illustrative of preferred embodiments of our invention, but it is not intended to limit the invention thereto. The proportions given are by weight. 80

## EXAMPLE 1.

1 part of glycocyamine, in powdered form, is thoroughly mixed with 4 parts of betaine hydrate, in powdered form, so that a homogeneous mixture results. 85

It will be noted that the methylating agent, that is, betaine hydrate, is provided in excess of the order of 4—1 over that theoretically required to react with glycocyamine to form creatine. At least 90 an equal molar quantity, per mole of glycocyamine, of betaine hydrate is

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necessary in order to assure that substantially all of the glycocyamine is converted to creatine, since it has been found that the presence of glycocyamine alone tends to cause liver disease (fatty infiltration). Preferably between about  $1\frac{1}{2}$  and about 5 moles of methylating agent, per mole of glycocyamine is employed. The other methylating agents named here-

10 in may be used in the same proportions.

The daily dosage of the mixture may vary over a fairly wide range depending upon the particular conditions and the patient being treated. Ordinarily the 15 amount of glycocyamine administered per day is roughly  $2\frac{1}{2}$  time that amount of glycocyamine normally formed within the human body through ingestion of a balanced diet. This excess amount of 20 glycocyamine is equivalent to about 30 mg. per pound of body weight per day. It is to be understood that the above-mentioned ratio of methylating agent to glycocyamine is always maintained; that 25 is, the methylating agent must be present in the mixture in molar excess per mole of glycocyamine. On the basis of 30 mg. of glycocyamine per pound of body weight per day, the dosage of the compositions set forth in Example 1 would 30 be about 150 mg. per pound of body weight per day. This amount is given in divided doses, preferably four equal portions, taken at spaced intervals during 35 the day.

It is preferred to administer the composition orally in the form of pellets and accordingly, the homogeneous mixture mentioned above is pelletized.

#### EXAMPLE 2.

40 1 part of glycocyamine, in powdered form, is thoroughly mixed with 5 parts of betaine hydrate to provide a homogeneous mixture.

45 The compositions set forth in Examples 1 and 2 have been given, in accordance with the treatment described above, and found to be effective in cases of rheumatoid and hypertrophic arthritis, gout, 50 heart failure, paralysis resulting from poliomyelitis, progressive muscular atrophy, and multiple sclerosis. On the basis of 30 mg. of glycocyamine per pound of body weight per day, the dosage 55 of the composition set forth in Example 2 is about 180 mg. per pound of body weight per day.

#### EXAMPLE 3.

60 1 part of glycocyamine, in powdered form, is thoroughly mixed with 3 parts of betaine hydrate to provide a homogeneous mixture.

65 The composition of Example 3 was given, with favorable results to patients suffering from heart failure, paralysis

resulting from acute anterior poliomyelitis, and gouty arthritis. On the basis of 30 mg. of glycocyamine per pound of body weight per day, the dosage of the composition set forth in Example 3 70 is about 120 mg. per pound of body weight per day.

The new therapeutic compositions of this application can be prepared by suspending in a liquid medium glycocyamine and a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine in the proportions set forth in any of the preceding Examples. 80

While we have fully described preferred embodiments of our invention, it is to be understood that we do not wish to be limited to the details herein set forth, but our invention is of the full 85 scope of the appended claims.

What we claim is:—

1. A therapeutic composition comprising a mixture of glycocyamine and at least an equal molar quantity, per mole 90 of glycocyamine, of a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.

2. A therapeutic composition comprising a suspension in a liquid medium 95 of glycocyamine and at least an equal molar quantity, per mole of glycocyamine, of methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine. 100

3. A therapeutic composition according to claim 1 or 2 containing a molar excess, per mole of glycocyamine, of the methylating agent.

4. A therapeutic composition according to claim 1 or 2 containing between about  $1\frac{1}{2}$  and about 5 moles, per mole of glycocyamine, of the methylating agent.

5. A therapeutic composition comprising a mixture of glycocyamine and 110 four moles, per mole of glycocyamine, of a methylating agent selected from the group consisting of choline, betaine, betaine hydrate, and dimethylthetine.

6. A therapeutic composition comprising a mixture of glycocyamine and 4 moles, per mole of glycocyamine, of betaine hydrate. 115

7. A therapeutic composition comprising a suspension in a liquid medium 120 of glycocyamine and 4 moles, per mole of glycocyamine, of betaine hydrate.

8. A method of preparing a therapeutic composition which comprises mixing glycocyamine and at least an 125 equal molar quantity, per mole of glycocyamine of a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.

9. A method of preparing a thera- 130

- peutic composition which comprises suspending in a liquid medium, glycocyamine and at least an equal molar quantity, per mole of glycocyamine, of 5 a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.
10. A method according to claim 8 or 9 which comprises mixing a molar excess, 10 per mole of glycocyamine, of the methylating agent with glycocyamine.
11. A method according to claim 8 or 9 which comprises mixing between about 1½ and about 5 moles of the methylating 15 agent, per mole of glycocyamine.
12. A method of preparing a therapeutic composition which comprises mixing glycocyamine and 4 moles, per 20 mole of glycocyamine of a methylating agent selected from choline, betaine, betaine hydrate, or dimethylthetine.
13. A method of preparing a therapeutic composition which comprises mixing glycocyamine and 4 moles, per mole of glycocyamine, of betaine 25 hydrate.
14. A method of preparing a therapeutic composition which comprises mixing glycocyamine and 4 moles, per mole of glycocyamine of betaine hydrate 30 and suspending the mixture in a liquid medium.
15. A therapeutic composition substantially as herein described with particular reference to any of the Examples. 35
16. A method of preparing a therapeutic composition substantially as herein described with particular reference to any of the Examples.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953  
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which  
copies may be obtained.